or is that not reasonable?

The second issue is the one that we had just started talking about when Dr. Bertrand had brought it up and the one that we had talked about this morning, is that we're looking at two clinical sites, and I find it quite interesting that the sponsor refers to this as an efficacy study, which I would argue with two clinical sites it is, in fact, an efficacy study.

But we're not talking about efficacy when we're looking at the **FDA**. We're talking about effectiveness. So the question of whether two clinical sites with one practitioner at each of those sites is an issue for efficacy which is not our concern here or is it an issue of effectiveness which is our concern?

And the issue of whether it's an issue of effectiveness, I think, has been addressed by most of the panel members and leading in one direction.

The third issue is the one about outcomes, which we had talked about when I had

talked about follow-up, and the final one is a pure statistical question which I had raised to the biostatistician at FDA in that the statistical assumptions are most likely not met for the statistical techniques that were done.

So then the question arises: would you have gotten the same conclusions if you had used the appropriate statistical test?

I don't know the answer to that because the sponsor didn't provide the data analyses analyzed using other statistical techniques. So I'm left with as much confusion as I had this morning. I was hoping to get some feedback from the sponsor and from some other panel members as to how we deal with some of these issues and how we think through some of the issues.

So, again, the issues are the follow-up, the site selection, and the practitioners, one at each of the sites.

The outcome measures and why we don't have inconsistency in terms of that, why were the patients not given the opportunity to fulfill at

least the paper and pencil assessments, and then the final one which is a purely statistical analytical question.

I'll stop at that point.

CHAIRMAN HEFFEZ: Thank you. Thank you, Dr. Janosky.

Dr. Li.

DR. LI: You're right. You may have already answered this in a previous discussion, but I might have missed it. How long did you estimate or did someone estimate it would take for you to get to 80 percent *of* 180 cases to reach three years?

DR. JANOSKY: Yeah. If I take a look at 180, and we can deal with that issue of cases versus sides versus patients, but let's just give them the opportunity to say that cases is 180.

If you take 80 percent of 180, you get 144, and then have 143 measurements at six months.

DR. LI: So it takes two and a half years then to get to three years?

DR. JANOSKY: Approximately, right. So 80 percent of their data are available for six

months worth of time. So on some level we can argue that there's six months worth of data available.

DR. REKOW: But can I?

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: Can I just go back? I agree with everything that you've said, but I also heard that the initial study was planned for only 68 patients, and I think we need to make sure we know what is the real basis that we're supposed to be using as our basis, and I don't know the answer, and it looks like Susan is anxious to tell us.

DR. RUNNER: Susan Runner.

I believe it was 89 -- 86. The initial IDE was approved with a projected number of 86, and that's the number that the original statistics were based on.

DR. REKOW: And that was to be 86 patients with three years' worth of --

DR. RUNNER: Correct.

DR. REKOW: Eighty-six cases or 86 patients?

DR. RUNNER: I believe when we sent an

IDE letter, we're talking about 86 patients. I mean, I think they interpreted it a little bit differently and changed it around, but we're talking basically about 86 people.

They then requested expansion of the study, and that's how we got to 300 approved, and they've gotten 180 operated at this point.

DR. JANOSKY: This is Janine Janosky.

I would postulate two things, Dr. Runner and Dr. Rekow, at that point. If that is the case, then what 86 are we going to take?

The sponsor didn't present to us data on only 86. So I would expect to see the first 86 or the 86 meeting inclusion/exclusion criteria, and their data presented separately. That would be the first concern.

The second concern, let's give them the fact that there was 86 and I'm assuming that that was based on statistical power analyses in terms of estimates.

Then what is 80 percent of 86? That's in the 60s. Do we have data on 60 patients for

three years? And the answer is, no, we don't.

So even if you argue that there's 86 in there, that you should have three years' worth of data on and taking an 80 percent rate, 20 percent attrition, you would expect 60-some patients with three years' worth of data, and we don't see those numbers.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

Simple question: were 86 people enrolled before January '99? I mean, that would give us a rough three-year follow-up.

How long did it take us to enroll those?

CHAIRMAN HEFFEZ: Would the sponsor come to the podium, please?

MS. VERSTYNEN: Mary Verstynen.

I believe that the first ***86*** patients enrolled will be out to three years in October of this year.

DR. BERTRAND: So it wasn't by January '99, January 2002 that you had ***86*** people originally enrolled. It took longer than '99 to get that many

in.

MS. VERSTYNEN: Right, and so it would have been in October of '99 that we had the 86 patients enrolled, and they would be at three years.

DR. BERTRAND: So in three months?

MS. VERSTYNEN: Yes.

DR. BERTRAND: Okay. So from that standpoint with 45, is there a way of figuring out how many of those 45 -- what date they were originally enrolled so that we could get an idea on that concept.

MS. VERSTYNEN: I can tell you in the first year of the study nine patients were enrolled, and then the study was enrollment stopped for a year's time period just to follow those first nine patients. So there was a real lag in the enrollment initially.

So I would say it probably took us -- I don't know that I could put an exact date, but enrollment started out very slow and has built tremendously in the last two years, and it actually built -- now, Dr. Sinn's patients first were at

three years. I believe was it in -- I remember. I remember he did it at Easter time. It was April '99. Was that when?

Did your first patients come out to three years this year or last year? Do you remember?

This year. Okay. So enroll really built then in April of 1999 when Dr. Sinn was added to the study.

DR. BERTRAND: So a lot more patients have been recruited since '99 than previously?

MS. VERSTYNEN: Yes, yes.

DR. BERTRAND: Okay.

MS. VERSTYNEN: I also want to state, too, as far as the sample size calculation that was originally in the IDE. Phyllis Silverman, we had worked with her in getting that sample size calculation, and at that point, looking at the literature, the outcome -- the delta of that calculation was based on a one centimeter improvement in pain, and clearly we see much more than that at the three-year time point

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: I guess my question, I guess, that Dr. Janosky -- at least what I have summarized in my mind what she's asking though is that given the fact that there appear to be an endpoint of when we would reach that number and we would have the three-year data for what was thought to be the original power or patient's number of studies, and we don't seem to be there, what prompted them?

If it was going to be in October of this year, we would reach that number. Why is it August and we're at that point?

And maybe Dr. Runner can answer that. What prompted the timing issue with this coming forward to the panel?

DR. RUNNER: I think the company needs to answer that question.

MS. VERSTYNEN: I can tell you exactly when that question was answered. It was at the last panel meeting in 2000, and at that point, both FDA and a Canadian official were there, and I had

printed out the proposed follow-up that we would have in the next couple of years.

Knowing that we had predetermined a cutoff of 86, I just showed them, okay, at this point we're going to have this many patients. At this point we'll have this many patients. At this point we'll have this many patients, and both FDA and the Canadian official said that when we had reached I think it was 49 patients at three years, that that would be an appropriate time to submit it.

CHAIRMAN HEFFEZ: Dr. Janosky.

DR. JANOSKY: Janine Janosky.

Ms. Verstynen, the number 49, what was that based on, the one that you just quoted, the number 49?

MS. VERSTYNEN: I went into our database and I picked, okay, cases that were done in a certain date. I just went back to the surgery dates just to see, okay, how many would I have at this time point. How many would I have at this time point?

DR. JANOSKY: Let me stop you for a

second.

CHAIRMAN HEFFEZ: Dr. Janosky.

DR. JANOSKY: Janine Janosky.

DR. RUNNER: Can I just make one comment? And correct me if I'm wrong, Mary. I know PMAs are supposed to stand on their own, and I believe that -- and you correct me if I'm wrong -- that your desire to comment came about because of the history of the numbers that were associated with the two previous PMAs.

MS. VERSTYNEN: Exactly. I mean, I guess I was proposing and figuring out how many patients we had had at different time frames, and looking and having been at the two other panel meetings, our number that FDA and the Canadian office set of 40 was far higher than the approved products.

DR. JANOSKY: Let me just follow up, please.

Janine Janosky.

Ms. Verstynen, typically we stopped studies based on criterion or criteria, depending

upon how many we have, objective stopping rules so that if something is very effective, we might stop it early because we can argue that we see much larger the effect that we possibly said.

So your number that you just said to us, that was not based on a specific stopping order; is that correct?

MS. VERSTYNEN: Correct.

Thank you.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

A question for Dr. Janosky. You've used the number 80 percent on several occasions, and I assume that that number is a number that one seeks in a clinical trial, but is that number necessarily fair given the nature of this trial, the nature of the patients, the nature of the multiple surgeries, and the psychological implications that go with patients suffering from this level of dysfunction? Is that fair to apply that number to this study?

DR. JANOSKY: I used the number based on a couple of things. One is typically what is the

response level that we expect to see.

The second, always if we're estimating a point, how many subjects do we need for a point estimation? So if we're looking at a specific type of confidence interval for a point estimation, how many subjects would we need based on a level?

So I'm sort of backtracking and giving them the benefit of the doubt.

DR. PATTERS: Let me then ask if --

DR. JANOSKY: So I actually would jack it up a little higher is what I'm saying.

DR. PATTERS: If we look at their patient accountability data which they provide on Table 8-7, they say that of the patients available at three years, theoretically available, 82 and a half percent of them are included in the data, which is 45.

If we go back for a year and a half, 89 of the theoretically possible 109 are available in the data. So if we assume that their losses don't change, you know, about roughly about 82 and a half percent of the patients are available. That would

mean that we'd have approximately 85 patients available within a year and a half.

Would you read that the way I'm reading it?

DR. JANOSKY: I would probably come to the same estimates, although those are only estimates.

This is Janine Janosky speaking.

DR. BURTON: Yes, I understand that, but regardless of how many they started with, 85 patients are a lot of patients for what they're doing. It may be only 50 percent of what they started, but it's a lot of patients.

Do you take that into account?

DR. JANOSKY: This is Janine Janosky again.

If you're going to argue that 50 percent is reasonable, then I would want to see data that shows me that those 50 percent that completed were no different than the 50 percent that did not complete. I don't see those data.

So when I don't see data that I expect

to see and I don't see a fair amount of data that I do expect to see, I need to wonder why. And since I don't have any basis to base anything on, say, okay, give me some hypotheses why I don't see this. Then I have to conclude that I don't know the answer.

So I can't conclude that 50 percent would be reasonable. So that's the quandary that I'm left with.

CHAIRMAN HEFFEZ: Dr. Burton?

DR. BURTON: I'm not sure this goes to Dr. Janosky or actually back to the sponsor, but in looking through this, it did state that you were starting marketing in Europe and obviously the PMA needs to stay and the IDE stands upon its own merits here, but also you've been marketing this device for at least greater than two years.

And I notice I've been reading. It was in South Africa. Do you have any supporting or correlating data from its usage in areas outside the country or at least any comment upon that?

Because it's interesting. I just thought it was done and there's nothing saying

numbers sold. Has there been with potentially less experienced people -- have you seen any other issues raised with that?

Because, again, I saw that at least that is occurring, but there is no reference beyond the fact that it is occurring.

DR. QUINN: Based on the Canadian approval and the CE approval, I have trained three surgeons, one in London, one in Sweden, and one in Toronto, who are well know, well experienced surgeons. I think the total number of cases among those three is approximately 75.

I don't have data on it, but that's the number of cases that's been done.

Might I comment on some of Dr. Janosky's? I think a few issues.

One, I appreciate your comment on partial data, and maybe it was my assumption that since these follow-up visits were radiological and face to face, that was maybe my misinterpretation that we weren't looking for partial data, and we either got data or we didn't.

I think there's about nine patients who actually were seen by an oral surgeon in another part of the country who did the face to face, did the X-rays, and we accepted that. I did not pursue your concept of partial data, which may have been helpful.

The other one is in looking at the -- and I know you questioned the term "efficacy" -- but in looking at the three primary efficacy points that we looked at, we did feel strongly that the data does tend to plateau between three and six months, and we were hoping that would be taken into consideration when looking at the percent of follow-up at three years; that they would be similar.

It may not address the issues Dr. Li raised, and I think they're important ones, but in terms of the efficacy or whatever term you'd like to use, I do think that's an important factor to take into consideration.

The other one in terms of early in the study of broadening this to multiple investigators and multiple sites, it was probably my reticence

that stopped the company. I had some severe reservations, I think it was difficult enough to control this in a very controlled environment. I think it would have been more difficult because, as Dr. Rekow said, there was an evolution. There were no events in this process, but it was an evolution, and I think that evolution was better controlled in a smaller environment.

CHAIRMAN HEFFEZ: Sometimes in studies such as this, data obtained from smaller sites is actually more valuable than data from bigger sites because you get to appreciate different indications, different surgeons' abilities, and that might end up sometimes judging the final usage, you know, of the instrument.

CHAIRMAN HEFFEZ Any other questions? Dr. Li.

DR. LI: Can I -- Steve Li -- can I switch gears and ask a materials and mechanics question?

One question I forgot to ask earlier, you're using titanium screws on a cobalt chrome

plate. In total joints we tried to list the last several years avoiding mixed metal contract because of crevice corrosion. For instance, we put a cobalt chrome head and a titanium stem. You'll actually find corrosion at the interface.

So my question is: do you see corrosion in these locations of mixed metal contact or, better yet, have you actually looked for corrosion at any point where the mixed metals are in contact?

MR. ROMAN: I can't answer that question from a clinical standpoint. I have not visually seen any of the explants. It might be something that Dr. Quinn can answer.

But as far as looking for corrosion at an interface between the titanium and the cobalt chrome, that's not something that we've looked specifically for.

I did want to say however, that we are using the or that the titanium plasma spray coating that's on the mandibular components is also a Titanium 64 alloy, and we have quite a bit of experience with this in the orthopedic realm and

have seen no problems with that.

DR. REKOW: This is Dr. Rekow.

Do you plasma spray the inside of the screw holes on the mandibular implant?

MR. ROMAN: No, no. It's limited to the ramal side of the plate.

DR. LI: Steve Li.

I would just suggest that you might want to look though where the screw holes and the screws interface because the crevice corrosion is often dictated by the size of the space and the local pH. So it's quite possible on your coating the crevices are of a certain size where you won't get corrosion, but if you switch the joint space, if you will, around the mixed metals, you could get into an area where corrosion is possible.

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: This is Dr. Rekow.

Dr. Quinn, can I ask you and Dr. Sinn a question, please? When you do any of the tissue revisions in the joint space for whatever reason, do you as a matter of routine look at those

histologically and immunologically, look for immunologic responses?

I know that that's an extra procedure. I know it's a lot of extra work, and I'm just wondering if you're doing that or not as a way to tease out whether or not you're getting any debris particles that could be an issue.

Because with some of your adverse events you're clearly going back into the joint space.

DR. QUINN: I think that has responded to Dr. Li's question this morning. We're doing histologic, standard histologic H&E staining. We haven't done specific immunologic testing, but I think it's not a bad idea.

But I should say coming from a macroscopic point of view, what we tend to see is fibrous encapsulation. It looks like a healthy fibrous glistening encapsulation. We haven't seen multinucleated giant cells or any evidence of polymeric debris, which would be consistent with polyethylene debris as well.

Again, the only foreign body reaction we

did get, and it wasn't done, was the corn starch.

There was one other question that I thought you raised and that I'd like to answer, and that was the difference between testing the bovine bone and testing on the human ramus.

We used 2.7 millimeter screws to secure the ramus. They come in eight and ten millimeters, and usually ten millimeters is beyond the bicortical width of the ramus. If anything, we have to back out a ten and put an eight in.

You can actually palpate when the tip of the screw comes through immediately. So in most cases we know we're engaging bicortical bone.

DR. REKOW: Thank you.

CHAIRMAN HEFFEZ: I actually would like to move on to the questions, and when the questions are discussed, I'm sure some of these issues will be revisited.

So all of the questions that are going to be asked to the panel are in your agenda book We'll try to get it on Power Point so you'll appreciate the question, but it's in your agenda

book.

The first question was or is: can the results for jaw pain intensity, interference with eating, and maximum incisal opening for the cases presented with three-year data, which represent 25 percent of the implanted population, adequately represent the expected outcomes for the total study group at three years?

Within this question, I think I'd like to ask the panel to consider that we're talking about cemented and noncemented cases. We have 11 noncemented cases at three years, but at this point in time the experienced surgeons are only placing noncemented prostheses.

We'll have to ask ourselves is the cement an important variable, and is it -- it may not be an important variable, and it is a variable that is now excluded in the noncement cases, and that could be a positive thing.

So I'd like to hear from the panel members how they feel regarding this question.

Dr. Hewlett?

DR. HEWLETT: Actually related to this question I'd like to pose a question to Dr. Li if I could.

Dr. Li, you raised some concerns earlier about the creep or potential creep around the screw holes in the fossa component. My question is twofold.

One, if as the sponsor has described a superior part of the fossa is routinely abutted against temporal bone, does that then lessen your concern about potential creep around the screw holes?

And, number two, do you feel that obduration of any potential dead space with the polymethyl methacrylate cement and thereby perhaps an increased surface area of contact between the superior part of the fossa and the temporary bone, would that then further limit any possible creep around the screw holes in your opinion?

DR. LI: Well, I think the fact that it's supported superiorally helps, but the screws -- and I guess a minimum of four screws -- are placed

because they're obviously felt that they're needed to hold the polyethylene in place.

But if there's no load on those screws, you then don't need screws, right? And the fact that you need a minimum of four tells me that either through empirical or through calculations, that they figure they have needed four screws to hold that polyethylene staple in place.

So that tells me that that polyethylene left to itself is going to want to move away from the bone. Otherwise you wouldn't need four screws.

Now, stress obviously is lower the more supported the polyethylene is, but it clearly isn't zero because there is four or maybe five screws. So I don't think that removes my concern about the creep, although the more supported it is maybe the longer it will take for the creep to get to a level of where you'll cause a problem.

I'm sorry. What was the second part of the question?

DR. HEWLETT: Well, the other part is do you think there's a substantial benefit to using the

cement inasmuch as it will increase the surface area contact between fossa element and the temporal bone.

DR. LI: Assuming that the gap or the space is -- there really isn't like a whole gap where the whole back is, you know, unsupported, and they're just like little pockets **of** unsupported area.

The one saving grace about polyethylene, in fact, is that it does creep and deform. ***So*** even if you didn't use bone cement, after a while the polyethylene I would suspect would kind of settle in eventually and kind of support itself.

So unless the gap is substantially large, I don't in my mind see why you would want to put cement in other than it **looks** better than it appears to be supported, which leads me to I don't have a great concern over the issue of whether or not the post was clipped off or not clipped off, unless you're going to think you're damaging the polyethylene somehow by the clipping.

But biomechanically in this particular application, I don't see a big influence of whether

or not there's a post or no post.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Dr. Burton.

I'd like to sort of answer that as well. I would agree with Dr. Li. When I looked at it from looking at it from my clinical experiences, I didn't think that clipping off the post made any difference, and I actually personally from my experience with cement felt that actually the fact that you modified the technique with a surgical burr to seat the fossa more accurately without the need for cement, and I gather from Dr. Quinn what they found was when they adequately contoured the fossa, they had adequate bone contact, and the volume that they were filling was so small that they were able to eliminate the cement, that I actually very candidly thought that was an improvement.

You know, you say, well, you have the earlier ones with cement versus noncement, and my guess is that probably eliminating the cement actually probably is an improvement unless from what Dr. Li sort of clarified, unless you felt that you

needed the cement for support, but, again, adequately contoured to get good approximation it would be supported.

And by eliminating that cement I think you're just candidly just eliminating one more variable. I don't think that the cement itself has any truly saving grace properties that make you want to have it in there.

So my estimation, when I looked at this before coming here and hearing the other comments, was that that actually was an improvement, not a detractor to the change.

CHAIRMAN HEFFEZ: Dr. Cochran.

DR. COCHRAN: David Cochran.

I would reinforce exactly those comments based upon our experience in periodontal surgery as well, using a number of different agents, cements, infurcations. I felt the fact that they did away with that was probably an excellent move on the sponsor's part in keeping it simply and just the components.

Well, the bone is going to react

obviously to the trauma of flattening. You're creating an acute wound, and I think that's where you get some of that hypertrophy of the bone tissue. So I think that as it is without it, it's fine. Also the clipping of the post, I feel like that very little influence on the device as well.

CHAIRMAN HEFFEZ: *So* let us just summarize this point then. We're saying that the data of cemented and uncemented can actually be combined. Is that the general feeling of this panel?

Okay, So let's come back to the question then. Do we feel that the data that's available **is** adequate, just to summarize the question? The question is up there.

Dr. Patters?

DR. RUNNER: Can I interrupt for just a second? You basically answered question number four. **Is** that -- you started with number one, but you sort of answered number four.

CHAIRMAN HEFFEZ: Well, question one involves number four. *So* that's why I brought it.

We're still on number one, but --

DR. PATTERS: Let me try to deal with question number one. I feel like using a percent to say this is only 25 percent of the data is not fair to the sponsor. I think the sponsor needs to be complimented on conducting what I feel is an obviously scientifically valid clinical trial of which all the data is not presently in.

I think the real issue is are 45 cases at three years enough to conclude safety and effectiveness. I don't know the answer to that, but I don't think it's fair to take a percentage, like 25 percent, and say, well, they've only got a quarter of the data. So it's not enough.

The question is: they have 45 cases now. It appears that they should have 85 cases no less than a year from now, maybe a year and a half from now. How many is enough? I'm not prepared to say, but overall I think that sponsors have taken a very valid scientific approach, and I think they're to be complimented.

It would seem to me that most of the

compliments go to Dr. Quinn for conducting what appears to be an excellent and unbiased trial.

CHAIRMAN HEFFEZ: I think we shouldn't focus on the 25 percent, but we still need to answer the question. Do we feel the data that **is** available at three years is adequate enough to predict an outcome?

Dr. Rekow.

DR. REKOW: This is Dr. Rekow.

I would like to have a little discussion about a little bit different spin on this. When I looked at all of the primary outcome assessments, I didn't see very much change after maybe six months and maybe even shortly after three months.

And so how much new information could we anticipate getting even if there were hundreds of more patients from what seems to be the trend at six months that continues to three years?

And I'd like to hear some conversations about that.

MR. SCHECHTER: This is Dan Schechter.

I know this application is supposed to

stand alone, and of course, it does, but as the sponsor noted, similar devices have had less patients involved, and those were approved, and in a sense, if we consider more and more patients, other than the 45 that have already reached the three years, we're in a sense penalizing the sponsor for extending their ID and getting more people involved.

Had they not extended it, the total study group would be much smaller and maybe we would be more willing to just accept the 45. So I think we should keep that in mind that the fact that they're extending this and that very few have gone beyond six months in some sense is a good thing. It means that it has so far been very successful, and FDA is willing to extend that.

But don't penalize the sponsor for that.

MS. HOWE: Elizabeth Howe.

My concern about the number and the amount of data is that there can be additional data collected fairly simplistically; that if we're talking about answers that could be generated by mail or if it could be done at another location and

submitted to the researcher there, in fact, ***is*** more data out there.

The question is: would those numbers make a difference?

And with such small numbers, it in fact could make a difference.

CHAIRMAN HEFFEZ: Dr. Cochran.

DR. COCHRAN: David Cochran.

You asked the question what more would you gain, and my concern still is obviously Dr. Quinn is a very talented surgeon, and we're thinking about safety issues, and you've got one surgeon who's very gifted with a reasonable number of cases at 30 years, but the additional data I think you're going to get is the variability between surgeons, and clearly when the device is approved, there are going to be a lot of people that use it and hopefully a lot of people wont use it that shouldn't be using it.

So I think that's where the additional data would come from, is can an average, if you will -- nobody wants to be called "average" -- but an

average oral surgeon be able to use this device and have the same results as someone as gifted as Dr. Quinn?

The other **is** -- I lost my thought. Sorry.

CHAIRMAN HEFFEZ: May **I say** something? That's really addressing question number two. I think we should just specifically **ask** if this information that we have now available for three years can give us enough confidence that this outcome will be reproduced in the following years, and that's the biggest question for those issues.

Okay. So Dr. Patters.

DR. PATTERS: Mark Patters.

I'd like to address Dr. Rekow, who I think brought up a very valuable point. **It is** not necessary in my mind that the sponsor answer these questions at only the three-year data point, and the fact that there seems to be little change in the data after three to six months, to me the panel should consider that information.

As to whether that additional

information had shorter time periods give evidence towards safety and effectiveness, and I think Dr. Rekow's point is an important one and needs to be considered by the panel.

The three years is as arbitrary. It's an arbitrary number that **FDA** recommended in a guidance document, but that doesn't mean that the data that's not three years old should be ignored.

DR. REKOW: Can I clarify one point? I want to make sure that you --

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: I'm sorry.

I want to make sure that you understand that when I raised that point I was talking about these three parameters of the pain intensity, the eating, and the incisal opening. I clearly think there are some issues related to adverse effects that have other implications.

I wanted to focus the discussion on this from the data that we've seen, and that's where I wanted to have this conversation at this moment to go.

CHAIRMAN HEFFEZ: Dr. Li and then Dr. Burton.

DR. LI: Just a clarification question. For question number one, what are we supposed to consider the total study population?

DR. RUNNER: This is Susan Runner. We consider the total study population the 180 cases that have been implanted.

DR. RUNNER: Thank you.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: In response to that question about the data, I think that for the three presented items I think you probably can because it appears that at that three to six month point that they reach I would say a stable endpoint, but the numbers don't really seem to change.

I think the question is that not having an adequate number out. In looking at previous and other implant systems and other surgical techniques that involve things similar to this, many times we didn't start to see those.

The other problems, other than the pain

and opening, started to appear; at least my experience was in that 18 to 36 month point was when you started to see more of the other potential, quote, unquote, complications appear.

So, yes, for those particular outcomes it probably is adequate at this point because I think we can extrapolate that out. The real question is for the overall device. Does that give you the same confidence?

And I'm not sure I have quite the same confidence for the shortness and the numbers relative to that as I do for those three variables.

CHAIRMAN HEFFEZ: Ms. Helms.

MS. HELMS: Yes, Elizabeth Helms.

I just want to make a comment. I would certainly like to see a higher percentage, and I certainly think that we as patients need to be more accountable especially when we're going to enroll in a study; that we should be following through all the way to the end.

But one of the points I wanted to make is you can be also assured that if the patients that

have these surgical procedures done were having problems, you'd be hearing about them. If their pain had increased, you'd be hearing from them because they don't pick up the phone, you know, when everything is good, but they sure do when everything is bad.

CHAIRMAN HEFFEZ: That's really not always the case in clinical practice unfortunately. Sometimes they don't want to hurt the doctor's feelings. Sometimes it's a financial reason. There's multiple reasons.

DR. BURTON: I guess having been involved with a number of studies and with both TMJ implants and TMJ surgery, I actually would agree with Dr. Heffez. I think it's almost the opposite.

There are a lot of people who when they become dissatisfied go to someone else, and I will be honest. I've had a couple of people in the last month who had had other implants done at other points. I said, "Well, have you contacted your original surgeon and discussed this, you know, these burning issues with them?"

And the response is invariably candidly been, "No, I have not."

And these patients candidly were 18 to 24 months out, and they said, "Yeah, I was doing really well. I moved. I haven't gotten back."

Have you called and told them and discussed what's going on here?

And the answer has been **no.** ***So*** I get a little antsy personally when I say, "Well, they're just gone," and so they're going for geographic success. The truth is that an equal number of those may be geographic failures.

CHAIRMAN HEFFEZ: ***So*** I'd like to bring back the panel to this question. Okay? ***So*** I'm going to -- you see the question up there, and we've got three things here: pain intensity, interference with eating, and maximum incisal opening.

I am going to try to summarize what the panel said, and I'd like to hear if the panel is comfortable with what I've said.

The data that is presented does and we do feel it can be extrapolated for these points and

we can expect that the outcomes will continue. However, it would be satisfactory to us if the company made an effort to obtain the additional data that it can do through mailings, and that we may see some variability in there, and that the company should, of course, continue to collect data.

But given this, these three points, that the data that's been presented does adequately reflect expected outcomes.

Would this be acceptable to the panel? I'm not trying to put words in anybody. I'm trying to summarize it so the gastric juices get satisfied.

(Laughter.)

DR. BURTON: Richard Burton.

I would say yes. I think given the parameters as you presented them, I would say yes.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

I concur with **Dr.** Burton and Dr. Heffez that, yes, it does.

DR. SUZUKI: Jon Suzuki.

I say yes.

CHAIRMAN HEFFEZ: Okay. Good. This is not a vote. We just sort of want to just get a general feeling.

I would like to jump to question four, and then we'll break for lunch. Okay? So let's go to question four.

The company plans to market the device that's noncemented or as a cemented fossa. In the clinical data set, some of the cases are with cement and some cases are without cement. Please discuss the data in light of these two different methods. Are there differences in outcomes?

So we previously discussed this issue, and that we did feel that we could consider the data of both the cemented and noncemented together, but I do think that I would like to ask the company. Mr. Pratt, is he in the room?

I'd like to ask Mr. Pratt: why does the company intend to market a cemented fossa when the two surgeons are not placing any cemented fossas anymore?

MR. PRATT: Joel Pratt with Lorenz

Surgical.

The objective was to provide the surgeons as many options, and if a surgeon felt that in a particular case cement was needed, they would feel comfortable doing so.

CHAIRMAN HEFFEZ: Well, we have now two experienced surgeons whoa re teaching this technique which we will talk about later as far **as** teaching modalities, but teaching the technique, and they're not teaching the placement of the cement.

MR. PRATT: That's correct.

CHAIRMAN HEFFEZ: I don't think I have to bring it any further.

Can you comment on that?

MR. PRATT: Dr. Quinn, would you tell us a surgeon not to use cement?

DR. **QUINN:** Peter Quinn.

I think this is more geared to the original application which used the term PMA cement or other media, and we were keeping in the possibility here, and I have strong hopes for this, that we will develop biologics and that sort of

calcium phosphates with BMPs in them or something more biologic that ultimately might fit an application here.

That was some *of* the reasoning, but if that's not acceptable to the panel, my feeling is that we will continue to place these without cement.

CHAIRMAN HEFFEZ: So there are specifics to what you just said, and I think Dr. Runner should address that from the FDA point of view.

DR. RUNNER: I think the panel has to be reminded that we have to take the application on what is in the application. We cannot approve something on the possibility that something will be developed.

So either you will cement with what you cemented or you will not cement with what you have not cemented.

(Laughter)

DR. QUINN: My opinion strongly is that this should be cementless. That is what we're teaching. That's what's working, and if we come up with another application, we'll have to **do** another

study in the future.

CHAIRMAN HEFFEZ: Okay. Thank you, Dr. Quinn.

I would like Dr. Sinn to come to the podium and also give us your opinion regarding this.

DR. SIN": Well, my --

CHAIRMAN HEFFEZ: Identify yourself.

DR. SINN: Doug Sinn from Dallas.

My experience showed that early on in the first six or seven patients that I did that the cement really didn't add anything to the case from my standpoint, and I actually was more happy once I took one pin off and just tested it, that I increased the stability much more by removing the pin than I did by adding the cement.

So I empirically discussed that with Peter, and we decided that we would try and make that change.

CHAIRMAN HEFFEZ: So you're both on the same platform.

DR. SINN: Absolutely.

CHAIRMAN HEFFEZ: Thank you.

Okay. Other questions from the panel? Dr. Patters, you had an earlier question or no?

DR. PATTERS: Mark Patters.

Dr. Heffez, you expressed my concerns far more eloquently than I probably could.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: My question then back to Dr. Quinn or to the individual from Lorenz.

Is the intent then or would you be more amenable to marketing it? Because obviously you removed the pin as of February this year. To market the device as an endless device without a luting medium, if you want to try to call it, whatever you would, Would that be your intent to market it that way rather than sort of as an either/or?

MR. PRATT: Joel Pratt, Lorenz.

I think we would be very comfortable marketing only for noncemented use based on the two clinicians' experience.

CHAIRMAN HEFFEZ: Okay. So now let us just summarize.

Are there differences in outcomes? We

feel that we can pool the data and that we're now talking only about a cementless fossa; is that correct?

Okay. Without any further comments, I think we can break for lunch and we would like to return precisely at two o'clock.

thank you.

(Whereupon, at 12:31 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(2:02 p.m.)

CHAIRMAN **HEFFEZ:** Okay. The second question that we need to address, I know we just finished lunch, but let's keep our attention to this. The second question is up there.

It's 132 of 180 cases were treated at site one, 40 of 180 cases at site two, and eight of 180 at site three and four and five. Does the fact that 96 percent, 172 of the 180 of the cases were treated only at two sites present a potential for bias in the clinical outcomes?

So I'd like to hear from the panel members. Dr. Patters.

DR. PATTERS: Mark Patters.

Of course it's potential for bias, but it works in both directions. It could bias the scientific nature of the project in a positive way and introduce far fewer variables. If there were ten sites and seven **of** the surgeons decided that in their hands they needed to put in two more screws than were in the protocol, then you'd be adding

variable upon variable upon variable, and I think to be commended here are the two sites that only added one variable of taking the cement and cutting the post off.

But, yeah, in ten sites there could have been ten variables added, and the scientific validity of the study compromised. So of course, it's a bias, but it works in both directions.

DR. SUZUKI: Jon Suzuki.

I wanted to comment also I agree with Dr. Patters. I think that the variables have been at least minimized. There's always variables in any clinical trial, but the fact that the vast majority of them were conducted at two sites I think minimizes those outside factors and probably for the statisticians' sake it makes things a lot more streamlined.

And I also asked the question earlier today regarding a learning curve, and we were reassured that there would be a significant training period or training sessions for those surgeons that are going to be using thee particular products. So

I don't think it's a problem.

CHAIRMAN HEFFEZ: Let me introduce a factor that I think that we should take into account, is that if there are only two centers to train people, is that feasible? That's something I think I'd like to hear how the other panel members feel.

Dr. Burton.

DR. BURTON: Richard Burton.

I think obviously that would be a significant thing, and the fact that you're not going to be on training might actually -- perhaps that should go back to Drs. Quinn and Sinn though. Do you have a feel I don't want to say what the demand is, but you know, are you going to be able to deal with the fact of being able to do that because, you know, again, what you were saying, Dr. Quinn, was that you were going to be or Dr. Sinn was going to be performing at least a surgery with these individuals when they started to utilize this system.

So, I mean, that's going to be sort of a

rate limiting **step,** if you want to look at it that way, to any type of marketing attempt by the company.

CHAIRMAN HEFFEZ: I just wanted to touch upon that point, but it's going to be really addressed in question 6(b). So if we can just stay on track as far as whether it's presenting a potential for bias just in the clinical outcomes.

Dr. Li.

DR. LI: Steve Li.

I'd just pass along kind of a story from the VAS spinal cage panel that I was on in orthopedics. There was a multi-center; I think it was a ten or a dozen multi-centers, a couple of dozen orthopedic surgeons involved in testing a spinal cage, and six of the two resident surgeons had a financial interest in the product, and the results from those six surgeons were about a **15** or 20 percent higher success rate than those that did not have a financial interest in the device.

Now, I don't think they were dishonest and the solution was not to give everybody a

financial interest to improve the performance, but I think the message though is they had a level of expertise or knowledge about the device that was not passed on to the very next generation of surgeons. So that was probably a very close training situation where the first six trained the next two dozen, and yet there was still a very large difference in success rate.

Now, I don't know if that translates to this or not, but it certainly raises the issue that two centers done by two expert surgeons would probably reflect the best possible outcome.

CHAIRMAN HEFFEZ: Well, we certain can ask Dr. Quinn and Dr. Sinn if they can come to the podium and do they have a financial interest in the selling of the product.

DR. LI: Well, again, that wasn't my point, I think.

CHAIRMAN HEFFEZ Yes.

DR. LI: Yes.

CHAIRMAN HEFFEZ Go ahead.

DR. QUINN: I'd like to answer that

question first. I have no patent in this. I have not received any stock. I have receive consulting fees over the past nine years, all of which have been donated to the University of Pennsylvania School of Medicine, Oral Surgery Giving Fund.

I have full intentions **of** being remunerated for time spent training other surgeons and putting courses on as a clinical service agreement, but actually with some great difficulty with the University of Pennsylvania Technology Transfer Center. We convinced them that it would be in the best interest to have Biomet maintain the patent on this device so that it's not held by me or the university.

To the issue of sites, Dr. Burton mentioned rate limiting. I'm somewhat in favor of rate limiting. I don't want the gate opened wide on this. I do think that we will broaden the site. In fact, the next proposed site is the University of Florida under Dr. Dolwick, who once he has training would become a trainer himself.

We try to identify sites based on both

the expertise of the surgeon and the geography because I think that's important for the patients involved.

I don't have a specific **gating** of how this would go, but to extend this from two to four to six gradually would be my preference and not to open this up widely immediately.

CHAIRMAN HEFFEZ: **Thank** you.

Dr. Sinn, could you answer *the* other question?

Identify yourself just before.

DR. SINN: Doug Sinn from Dallas.

I, too, have no financial interest, no patent, or no relationship with Lorenzo other than as a consultant, and have received compensation for reimbursement for training or for traveling and that's all.

CHAIRMAN HEFFEZ: Thank you.

Any other questions from the panel?

(No response.)

CHAIRMAN HEFFEZ: So if we could summarize this question, do we all feel or it

appears to me that we all feel that it doesn't really bias the clinical outcomes, and that in some ways it could be beneficial. Everybody more or less concur with that statement?

DR. PATTERS: I concur.

CHAIRMAN HEFFEZ: Okay. Very good.

We'll go to the next question. Fifty-two patients of the 168 implanted patients had reports of adverse events. Of these 52 patients, eight required permanent devise removal. Please discuss the rate of adverse events in this patient population.

So if we look carefully at the adverse list, you'll see that actually the reporting was quite generous, reporting things that weren't really directly related to the prosthesis itself, but related to the surgical approach, for example, to it.

So I'd like you to look at that adverse list as a panel, and do you feel this list of adverse events is inappropriate?

Dr. Cochran.

DR. COCHRAN: This is David Cochran.

I think given the population that we're dealing with, this is a very low rate, in fact, and I'm very comfortable with it.

(Pause in proceedings.)

CHAIRMAN HEFFEZ: Excuse the silence for just one moment.

Dr. Runner?

DR. RUNNER: I saw Dr. Burton and Dr. Eggleston nod their head. Could they make those nodded comments more verbal, please?

DR. BURTON: Richard Burton.

I as one of the oral surgeon consultants to the panel and having been involved with TMJ surgery for, I guess, 20 years now, actually I feel that both the rate and the reporting -- I'd have to agree. Actually Dr. Cochran was reasonably liberal in their approach to that because, again, many things that were worded as adverse events were actually what most of **us** as surgeons -- and I'm not sure patients like that term -- but are part of the normal, accepted things that go along with just the

surgical approaches to the joint or with any type of surgery whether it be infected, both the rates, the occurrence, and the resolution of those. We're certainly within the normal realms for this type of surgery, and in looking at the number of joints that had been lost within that time frame, with eight explanted joints out of that number, while certainly everybody wishes it was zero, it still is still historically looking probably a much lower number than most of us really would -- I candidly would have probably expected out of that population, even though the fact that this is not some ten or 15-year follow-up and in that amount of time, that is, again, both a reasonable number and a reasonable outcome.

CHAIRMAN HEFFEZ: Dr. Hewlett.

DR. HEWLETT: For me, in order to get a comfort level with this question, I tended to focus on the six reported cases that were deemed by the investigators device related because of the generosity, if you will, in describing the other adverse events.

And even within those, there seemed to be some circumstances that, looking at it objectively, could perhaps even be not necessarily related to the device.

So given that, six cases, all but one of which appear to fall -- the adverse events occurred within that three-year period. I would tend to concur with the other sense of the panel so far that this is an acceptable level of adverse events.

CHAIRMAN HEFFEZ: Okay. Thank you.

Now, I'd like to tackle this issue which is related to two and three, and I'd rather tackle it now because we'll need to tackle it later.

Related to two and three I'd like to ask the panel regarding the indications because the indications are related to adverse events, and it's related to clinical outcomes.

We've discussed already previously that the indications are covered over approximately 11 rubrics, and the point has been made that the testing has been primarily in certain rubrics, and I'd like to know how the panel feels where the

device has been properly tested, in which of those diagnostic categories.

So I enlist the panel members to look at the indications and give me their comfort level.

During the silence I can help out and say at least there's osteoarthritis, and one of the points raised was the fact that many of these patients have multiple diagnoses and a primary diagnosis wasn't assigned.

But if you look at the numbers, you're looking at osteoarthritis, traumatic arthritis, total implant, avascular necrosis, ankylosis. Those are the big categories.

In a previous question, Dr. Quinn -- and I'll ask him to come to the podium just to confirm this -- did indicate that he felt that he agreed that the prosthesis had been tested better in certain cases, such as osteoarthritis and in other categories less well.

Do you want to respond to that?

DR. QUINN: Peter Quinn.

I would just like to make the point that

I think in order to collect data we were trying to be very specific for the purpose of the study, to identify very specific diagnoses.

I think if you look at the two approved devices that are on the market, they both have the same indications, and I think there are five indications. They are much broader.

For example, one of the approved indications is loss of vertical height of conduct. That would cover any of these indications. So I think in an attempt to collect more specific data, we may have painted ourselves into a statistical corner.

And I would suggest and maybe ask Dr. Runner if looking at indications of approved devices would actually be better guidance.

CHAIRMAN HEFFEZ: I'll ask Dr. Runner to help in the situation because we're not allowed to look at another -- you know, your PMA has to stand alone, but I'll ask Dr. Runner.

DR. RUNNER: I would suggest that the panel take into account this particular device and

the indications that are listed on this device, and if you feel that there is not data, do you feel that you can extrapolate from the known condition to use of this device and whether that's appropriate or not?

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Richard Burton.

One question I had. I just noticed this because of going back and forth, but in our panel packets there's a summary of safety with respect to this, and it lists ten indications for use, and then the essential prescribing information, which is very, very similar lists 11, and the difference is that it lists a number eight, and to make it 11, but number eight says degenerated or reserved joints with severe anatomic discrepancies, which the indications for use in the summary sheet doesn't list that one.

So, I mean, I'm not sure. The first question is, and I guess it's probably back to you, Dr. Runner, is why there is a difference between the two, but I think that, you know, sometimes trying to

make a difference between whether it's avascular necrosis, a degenerative rheumatoid patients, or a degenerated or severely resorbed joint really are in reality all the same thing.

So, I mean, I would actually -- I think Dr. Quinn may be correct here, in the fact that the specificity may not really be the **issue. I** think it's the degree of deformity, the degree of disability that the patient has is really probably the driving factor in making the decision to move toward some kind of a joint replacement as opposed to a more conservative procedure and whether it fits one of those specific categories may not be the best system of classifying it for that.

But can you answer why there's a difference between those two lists?

CHAIRMAN HEFFEZ:

DR. QUINN: I apologize for the discrepancy. I wasn't aware.

DR. RUNNER: This **is** Susan Runner,. In terms of our review of the PMA, we looked at the indications for use list. The summary of safety and

effectiveness is typically a document that's submitted by the company and is substantially revised at the end of the review process. So that really was not reviewed in detail.

The indications for use that was submitted with the PMA would be the primary indications that we went through for our review.

CHAIRMAN HEFFEZ: I have, Dr. Quinn, a question. If you look at the indications, in general they are all similar in the sense of lots of vertical dimension. One of them always that stands out is the development abnormality, and how many cases actually were treated with developmental abnormality to your knowledge?

DR. QUINN: I can't recall any that actually fell into that, offhand that **fell** into that category.

CHAIRMAN HEFFEZ: Dr. Patters.

DR. PATTERS: Mark Patters.

It appears to me that Dr. Quinn has pointed out that there is no reason to believe that the device would behave differently in indications

which were not studied, but I think it's only appropriate that the sponsor indicate in the labeling that this use has not been studied, and there is no data. That would satisfy me.

There's no reason to think it would behave differently, but there is no data to say that it, indeed, does or does not.

CHAIRMAN HEFFEZ: How do the other panel members feel about Dr. Patters' statement?

You can sit down, Dr. Quinn. Thanks.

DR. BURTON: Richard Burton. I would agree with Dr. Patters on that. In our summary package, Table 2 was diagnosis, and it lists out 11 diagnoses some of which have been grouped within those surgical indications because the arthritides are grouped as one group, whereas they split out all three of the arthritides separately as part of their percentages, and it appears, at least looking at the diagnosis table, that there are listed indications in terms of surgical indications that thus far there have been no cases presented that fit that diagnoses.

But I think that what Dr. Patters and I would agree with is the fact that given the fact that these are all functionally equivalent in many respects, that you would not expect that this device or any other to perform any differently given the clinical environment that they're in because clinically though the origin of the problem may be different. It probably would not affect the device itself once it was implanted.

CHAIRMAN HEFFEZ: **So** let me -- Dr. Runner?

DR. RUNNER: I just wanted to remind the panel that you can feel free to make recommendations about a more general indication for use or more specific as you see fit.

CHAIRMAN HEFFEZ: I'd like to maybe summarize the panel's position here and, please, I would like to hear from the panel how they feel.

We feel that the indications that the -- that the devices indicated for replacement of the temporomandibular joint and it has been well studied for perhaps loss of vertical dimension in

osteoarthritic, traumatic arthritis, avascular necrosis, ankylosis, but additional studies need to be developed in order to study it in other diagnostic categories, to replace other diagnostic categories.

DR. RUNNER: Question. Are you stating that you feel additional studies need to be completed or you would prefer a labeling?

CHAIRMAN HEFFEZ: A labeling. I'm sorry.

DR. RUNNER: A labeling that would say that it has not been studied in these conditions?

CHAIRMAN HEFFEZ: Dr. Runner, I agree, a labeling saying that the device has not been studied adequately for those other rubrics.

How would the panel feel regarding that? Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

I think having a caveat that in certain conditions there's been some data and in other conditions there isn't enough patients with that diagnoses had that labeling, I think it would

suffice.

CHAIRMAN HEFFEZ: Okay. I've got a general consensus on that.

Now, there's one other point related to two and three that I want to cover, is that in some cases part of either the fossa, in most cases the fossa, but either the fossa or the condylar prosthesis was removed for reason X and that patient went through a certain period of time before receiving the other portion of the joint, prosthesis. In other words, they're walking around with a partial joint prosthesis. Is there a recommendation when that has to be replaced or is it adequate to let them function with a hemiprosthesis?

I'd ask Dr. Quinn or Dr. Sinn to address them.

DR. QUINN: We clearly don't believe in hemiarthroplasty as a general indication, but I think there are time periods that are determined by the cause for the initial removal. For example, in infection, and Dr. Sinn had a patient with MRSA that he can comment on, but we have reimplanted them up

to two *years* later, and as short as three months later when the tissue condition improves to the point where it would be safe to reimplant it.

I'm not sure we could put a time period on it, but I think we could say there should not be permanent hemiarthroplasty indications.

CHAIRMAN HEFFEZ: **So** have **you** seen any adverse effects from waiting in a delayed fashion on those few cases prior to replacing the glenoid fossa, for example?

DR. QUINN: It was not a great n, but I think the biggest problem is deviation of the mandible to the side of implant removal. If there isn't gross deviation and, again, in multioperated patients where they're scarred, they tend not to deviate as much as somebody who has a de novo fractured condyle.

If there was gross deviation, and based on the deviation there was malocclusion and pain, I would tend to replace it sooner than later, but we have replaced them up to two years later.

CHAIRMAN HEFFEZ: Thank you.

DR. **QUINN:** Can I ask Dr. Sinn to comment on his patients?

CHAIRMAN HEFFEZ: Dr. Sinn.

DR. SINN: Dr. Sinn.

The explants that I was involved **in,** one patient, as Peter mentioned, was a methicillin resistant Staph. infection, and that particular patient was a nurse in an emergency room *and* probably a MRSA carrier, and the explant was done both top and bottom on one side. The opposite side was left to function. It was not infected.

It was replaced three months later when we had tag white blood cell scans that were negative, and it got infected a second time and, in fact, explanted on the same side a second time., and it remains out to this day, and it's been about six or eight months since I took it out, and the patient is begging me to have it put back in because of the dysfunction that's associated with it.

But I've had no explants where I did partial removals. So all of mine have been complete. If I did, I did three.

CHAIRMAN HEFFEZ: Okay. Thank you.

So I'd like to have a consensus from the panel that this device is -- as far as labeling is concerned, that we should consider not recommending it for partial joint replacement. How does everybody feel about that?

DR. PATTERS: Excuse me, Dr. Heffez. Mark Patters.

In the labeling that I see in all capital letters they say, "Do not use the individual components for partial joint reconstruction. So it's quite clear that they're insisting that it be used only as a total prosthesis.

CHAIRMAN HEFFEZ: All right. I'd like to move now on to question five.

The sponsor has provided engineering test data and a protocol for testing on both the new fossa design without a post and the fossa with a post removed using a rongeur. Do the engineering test data and protocol as presented given adequate safety and effectiveness information on the device?

Now, I understand that the information

regarding the post being removed is to be forwarded to the **FDA,** but we haven't received that as of yet. If we presume that that information concurs with the data with the post -- I'd like to ask the question that way -- is the data providing adequate safety and effectiveness?

I'd like **to** hear from Dr. Li.

DR. LI: Steve Li.

Actually I'm not sure the test is meaningful in either case. It seems to be unidirectional loading that doesn't ally place the post anywhere in a biomechanically important function. So I think this particular test is not effective evaluating the device.

Secondary to that is as I said earlier I don't really think the presence of **post,** removing that post actually has serious or actually any biomechanical effect.

As long as I'm talking, can I raise things about testing or **is** this not the time to do that?

CHAIRMAN HEFFEZ: No, that would be a

good time.

DR. LI: I guess I would rather see them test the things that I think are the big question marks in my mind. That would be obviously the wear issue, the polyethylene wear issue.

I'd like to test this concept of creep of the polyethylene around the screws that fits the polyethylene to the glenoid area. I just can't believe that those don't loosen in time. Maybe the amount of loosening is not clinically detrimental, but I would be very surprised if this happened at all.

And a third, much less important, I think we should at least check whether or not there's any chance of mixed metal crevice corrosion by using titanium screws against a cobalt chrome plate.

I think those three would be important features.

Also I think the screw pull-through test with the polyethylene also is not a clinically meaningful test. I think if you want to do that

test, you might do it in conjunction with a pre-test. That would be the load to the flange, to the polyethylene flange and see if that actually causes creep because that's how it's going to pull through and loosen.

Once it gets to a loosened point, it's going to be loose. It will probably never really pull all of the way off the screws, but it could become loose to the point that it would be either poorly functional or nonfunctional.

So those would be my suggestions for additional testing.

CHAIRMAN HEFFEZ: While we're discussing this I'll ask Mr. Mulry or Dr. Mulry -- I apologize -- to circulate the device around the panel **so** that they can actually touch and feel it.

MR. SCHECHTER: This is Dan Schechter.

I don't know if anybody with the sponsor can answer this question, but can anyone comment on how the testing done on this device compares to the similar devices, namely knee joint or hip point that has been mentioned a couple of times here today, how

the testing compares at all specifically in terms of the specific tests that were done, pull through, et cetera.

MR. ROMAN: Shawn Roman.

Just to make sure **I understand** the question here, you want to know how the test results are --

MR. SCHECHTER: Not necessarily the test results, but the battery of tests needed in terms of a pull-through test, a T test. It was mentioned before that there was no or that you don't have a good fixture model to simulate TMJ motion. Are there fixtures like that for a knee joint that you use, just as an example?

DR. BERES: Ken Beres from Biomet.

I think in terms of the testing that was done, it's really a look at failure models, and we particularly ought to take fracture or failure modes.

And so you run it through the T tests and see does this flange break or does that break? And those tests are done, and these obviously and

HIPS for a situation that mimics their use. Similarly, when we did a T test, we put it in a mock-up of a TMJ and you cycle it through ten cycles, which are really for just breakage.

The idea of wear testing is a very good one, and we do that with hips and knees where there are simulators especially designed for those joints, to give you an answer. TMJ, I'm not aware of anything close to a simulator that could get **us** that data. It's a great idea, but I don't know of a machine that exists that would be capable of giving that data.

CHAIRMAN HEFFEZ: **As** far as the mechanical testing, I raised the point and asked if you had a comment on it before as far as many **times** you're testing all of this in vitro with the parts perfectly mated, but the value of testing it with them not perfectly mated, which would probably be a more realistic test. How do you feel about that? Would those tests be of value?

PARTICIPANT: I think that's an exceptionally important point. Even in the total

hip joint where the contact stress and perfectly aligned, there may be only ten *or* 15 percent yield strength of the polyethylene. If you put the cut at a high induction angle and you look close to the rim, the contact stress gets up over the yield strength of the material.

So that the alignment and how **the** mandibular point would contact the fossa would greatly influence the contact stress and resulting failure mode of the polyethylene.

And just as a follow-up to Mr. Schechter's question, I think in general my general feel is that your in vitro testing should mimic what's going to happen in vivo. At least two **or** three of the cases of the test that provided by the applicant a reasonable materials test, but even they realized that they are not in vivo related tests.

So they're kind of a good material engineering thing, but they don't really help the patient, and **so** my suggestions are to try to point the testing and direction so that a result will give you some clinically meaningful predictive bound.

There's almost none of that as relates to the polyethylene.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: Susan Runner.

Correct me if I'm wrong. The company did set up their fatigue test model in a worst case scenario with the mandibular portion canted; **is** that correct?

PARTICIPANT: That's correct. As mentioned in my presentation, we incorporated three different conditions into the fatigue testing which were used to simulate worst case scenarios, one of those being angling the mandibular component at ten degrees with respect to the fossa.

DR. LI: Steve Li.

Wasn't that a worst case scenario for the mandibular component? Wasn't it still aligned on the fossa side?

PARTICIPANT: Well, the nature of the design is for the spherical head of the mandibular component to align with the spherical head and --

DR. LI: I understand, but my point is

that the worst case scenario, the way I read their test description, the worst case referred to the mandibular side.

For instance, if you work perfectly -- I haven't handled the components, but I think Dr. Quinn said not perfectly performing. So there's a little bit of possible motion of the mandibular.

DR. QUINN: Actually the spherical head of the mandibular component has a smaller spherical radius than the --

DR. LI: Correct. ***So*** that gives the mandibular point of contact a range of places it could be, and some of those places are higher contact stress than others.

DR. QUINN: And that's why we had angled the --

DR. LI: But it wasn't clear to me that they were not mutually exclusive, but you could put you component at ten degrees and get contact with the fossa component at the exact same place, or did you when you moved the mandibular component change the location of the contact point to the fossa?

DR. QUINN: I guess for the testing the center lines from the spherical radii that made the components work were aligned.

DR. LI: That's your interpretation. So it was the worst case for the mandibular side, but not necessarily for the fossa side.

DR. QUINN: Again, I don't see the difference there between them. You definitely would have a smaller surface contact between the mandibular component and the fossa component. So it would be a worst case scenario for the fossa component.

CHAIRMAN HEFFEZ: To come back to that, what did you test for? What are the tests?

DR. QUINN: All of the **T** tests were done with that angulation.

CHAIRMAN HEFFEZ: Thank you.

PARTICIPANT: As I understand, maybe just to clarify, it sounds to me like Dr. Li's concern, which I think would be well founded, is that the test occurred and produced some pressure and did not try to replicate any sort of either

rotation *or* translational movement between the components.

DR. LI: That's correct.

PARTICIPANT: And I think that's the concern that's being raised.

DR. LI: And that -- I'm sorry. Steve Li -- that's exactly right, and also ***the*** location and the contact. In other words, as Dr. Rekow *just* handed me the components, if I could use my hands as the components, the mandibular component is here or it could be here, and the closer it gets to the edge, the higher the stresses get on the polyethylene.

So I would keep this contact area constant and change my mandibular component **a** long way, but yet if I don't move the location of contact, my contact stress on the polyethylene is the same.

So unless they specifically move the contact points as they move the mandibular component, they're putting the mandibular component in the worst case scenario, but not necessarily the

polyethylene.

CHAIRMAN HEFFEZ: Yes.

MS. HELMS: Can I answer that?

CHAIRMAN HEFFEZ: Please identify yourself.

MS. HELMS: Elizabeth Helms.

I can answer that worst case scenario because this would be one of my questions and my key scenario. Ankylosis of the right side, healthy joint on the left side. The ankylosis caused the left side to take the entire load, and the condyle went up into the fossa of the bone until it broke through the disc and then broke through the bone of, you know, the fossa.

I can't tell you the excruciating pain that's involved when you lose, you know, both sides like that, and so Dr. Li's question, I think, is really valuable because if you have a case scenario where you have one side that has a loss, what's going to happen to the condyle as it hits up into what is it, polypropylene? Is that right?

What will happen to that with that, and

that's an intense load on the site, and you know, would it be fair to say that that kind of test has been done *so* that you would have a response because that is something that can happen in many cases.

CHAIRMAN HEFFEZ: Any further comments from the group?

DR. FAULK-EGGLESTON: This is Dr. Faulk.

We don't have a comment. We *just* had a question now that we've seen the device: why the indentation is on the top surface even on the site that doesn't have the little indented letter P or Y is there?

MR. ROMAN: All right. That is an undercut groove of those included in the design to give an area for securing a bone filler or bone cement that does not extend above the top surface of the fossa component.

DR. FAULK-EGGLESTON: But now you're not putting in a bone filler.

MR. ROMAN: That's correct.

DR. BURTON: *So* Richard Burton.

So my question is, you know, it may not

make a difference, but wouldn't you just have a smooth surface up there? It looks like it was an undercut obviously for retention, and you know, you eliminated the post offer here, but retained that.

MR. ROMAN: Yeah, I agree. Since we've discussed offering it as a cementless device, that undercut groove does seem unnecessary at this point.

CHAIRMAN HEFFEZ: However, these devices have been marketed and used and studied; is that correct, the cementless devices, since February?

MR. ROMAN: Yes.

CHAIRMAN HEFFEZ: Dr. Hewlett. I'm sorry.

DR. HEWLETT: I was just going to say or suggest that given Dr. Li's concern and the ensuing discussion that perhaps we've identified a potential condition for approval that might be the appropriately discussed further during the voting.

CHAIRMAN HEFFEZ: Yes, but I think that if we could address this question right now specifically, I think we could say, if I can summarize what I'm hearing, that additional test

data should be done in order to demonstrate adequate safety and effectiveness.

There were certain questions that were raised regarding where creep and mixed metals. Those were the -- now, how does the panel feel?

Dr. Runner?

DR. RUNNER: **This is Susan Runner.**

The question would be if the panel could discuss whether this testing needs to be done pre-market or post market.

CHAIRMAN HEFFEZ: **All** right. We could discuss that during the voting, but I guess we could ask: do the engineering test data and protocols presented give adequate safety and effectiveness information on the device as it stands?

How do people feel about that? Dr. Patters?

DR. PATTERS: Dr. Patters.

It appears so in my mind, and since they report no failures of the device in the **180** cases that it has been planted in, I feel pretty confident that the device is safe.

CHAIRMAN HEFFEZ: Dr. Bertrand?

DR. BERTRAND: Peter Bertrand.

Is that over a three-year period or longer, or are we restricted to a three-year period?

I know that Dr. Quinn's group **and Dr.** Sinn's group are continuing to collect data in three and four years. So we really don't know long-term effects yet, but over three years it does appear that it's fairly safe, but are we looking at it as far as making a judgment at three years?

DR. RUNNER: This is Susan Runner.

I think that for the purposes of this panel meeting we should look at it in terms of how the study was designed for three years.

CHAIRMAN HEFFEZ: So, Dr. Patters, you're --

DR. ANSETH: Dr. Anseth.

I just had a quick question for Dr. Li.

I think you had brought up some of your experience with the hip and knee implants, and based on the long history of using the ultra high molecular weight polyethylene and the cobalt

chromium alloys, could you comment on if there were excessive wear, would they have seen anything, any other indications after three years of this study?

DR. LI: It's possible had they looked more carefully, for instance, with a more focused or more specific idea on the histological sections, perhaps closer view of the retrieved polyethylene components, perhaps even further analysis of the in vitro tests, had they made some more measurements on the laboratory test specimens. I think all of those were three potential sources of getting some idea of how much wear and damage is occurring.

But my concern is none of these measurements were made. So they may or may not be a problem. I guess that's my question or that's my concern.

DR. ANSETH: But in general, if wear becomes a problem is it seen later, so after? So would three years be on a very short time scale?

DR. LI: Three years would be on a very short time scale for something like osteolysis. You would have to have an enormous amount of wear, but

we have unfortunately on the orthopedic side, I can think of three instances of devices that look great at three years, and there was a line for revisions at five because we just don't understand the wear rate. We just didn't see the wear rate at three.

CHAIRMAN HEFFEZ: Dr. Rekow.

DR. REKOW: Dr. Li, I want to ask you another question.

I agree that wear is a potential tremendously important concern. I don't know enough about the orthopedic literature to know if you get wear data and you can characterize the wear patterns and you can characterize the size of the particles, is the state of the science sufficiently well defined that we would know what those imputations are likely to be?

I have no trouble asking people to do more studies, but if we don't know what the outcomes of the studies are, I'm reluctant to impact their business for something we might not have anymore information other than some esoteric answers.

DR. LI: Steve Li.

An excellent question. I think all I can tell you quite honestly, in the laboratory, in vitro testing side is we've got tests that will tell you if you're going to be in really bad trouble. We don't really have a test to say if you're going to be okay. So therein lies the problem.

So at this point though, it's possible to be kind of in a not okay situation at two and three years and not really know it unless you actually go out of your way and look a little harder.

So I'm just worried that, in fact, it looks great. In fact, the data looks great at three, but you run into things we've seen before that all of a sudden at four and five you've got a large revision business because of osteolysis.

Now, I'm not saying that's the case here. I just don't know.

DR. REKOW: As a follow-on question -- this is Dr. Rekow -- now I've forgotten the question. Are there any ways that you can effectively accelerate the test so that in vitro you

could accomplish more cycles with heavier loads or something that gives you the same sort of things at least in the knees and hips in a shorter time span, that essentially gives you a worst case, but you could extrapolate a different time span than the three-year clinicals?

DR. LI: Those are really the descriptions of NIH grants actually.

To be fair to the sponsor, as far as I know, there is no, in fact, currently available TMJ simulator. However, the device has been around since the early '90s. In the early '90s there were no knee simulators either.

So for some reason this particular area has not devoted their attention to building one, but certainly there are no more degrees of freedom in a TMJ than there are in a knee. So it is a possible thing to construct, but *you* might not have to go that far.

I mean, certainly looking with 180 devices out there, there might **be** enough clinical information from retrievals, histological sections,

maybe pick a subset of groups to do a more close radiological study.

There are options where you can get a clinical sense for how much wear is going on. I guess I would like to see some measure of that, if not right away in the laboratory, at least some program to try to determine what level of wear they've got.

CHAIRMAN HEFFEZ: In the in vitro testing that was done, would you have expected to see where?

DR. LI: No, that's one of my concerns I saw none of the in vitro tests that would actually, or at least the way they conducted the tests, that give me any indication of wear or creep results in there.

So it's possible had they done a similar work and made extra measurements they could have answered some of these, but the testing done so far, I think it's kind of an odd thing. The testing says the device is okay. The clinical results say at three years the device is okay. But I don't think

they really had anything to do with each other

In other words, I don't think a laboratory test really dictated or predicted the clinical situation.

CHAIRMAN HEFFEZ: Dr. Cochran.

DR. COCHRAN: David Cochran.

I think one of the things we have to keep in mind though is the function on these particular joints. As was pointed out in the data, a lot of these patients have had five surgical procedures before this, and you've got 45 cases at three years with, as Dr. Patters pointed out, no indication of failure in any sort of way.

So although some of the in vitro testing would certainly be nice to see, I don't see that as a real necessity for us to go and make a decision in this case.

CHAIRMAN HEFFEZ: Dr. Burton.

DR. BURTON: Richard Burton.

I would agree with Dr. Cochran on that. I mean, I think that it's interesting. I can tell you that there's a bioengineering group at our

institution who has looked actually for three or four years now trying to come up with a simulator with numerous attempts at things, none of which have been very successful

I mean, I think it can be done, again, if you're looking for grant money to try to do something like that, but again, trying to correlate what you might find in vitro with what we have at least found thus far in the clinical population doesn't appear that we're going to gain enough certainly at this juncture that would aid us making a decision either way.

I think, you know, we probably all hope that we will find some method where we can provide more adequate testing, and unfortunately at this juncture it doesn't exist, and I can't see how we can ask the sponsor to sit there and say, "Yeah, we ought to come up with a test, but we're not really exactly sure what it is and we're not really sure what we're going to find, and we're not sure what the correlation is going to be with what we find with the clinical presentation.

CHAIRMAN HEFFEZ: I will leave this question, but I want to just leave one statement, which is that the question is addressing the engineering test data. It's really not addressing engineering test data and its relationship to clinical data. It's specifically addressing the engineering test data.

So I just leave that, and then we'll come back to it when we look at conditions.

Six (a), draft labeling has been submitted by the sponsor and reviewed by the FDA. Please discuss the draft labeling as presented.

Labeling is in -- everybody familiar where it's located? It's located in the back of -- the industry rep. and the patient rep. do not have this, but it's in -- for the panel members, it's located in the panel packet, one of the orange tabs. It's tab number three.

For industry rep. and patient rep., tab two.

The labeling from the sponsor describes a description of indications, contraindications,

warnings, precautions, adverse events, clinical studies, how it's supplied, sterility, and it has a second section that describes patient information

So let's look at the first section, which is the actual prescribing information. I'd like to hear from the panel members.

DR. BURTON: Dr. Burton.

I have a question for Dr. Runner. You know, it made the comment in the question that these have been reviewed I would assume by your staff. You don't state much of an opinion, but the indications, like I said, are listed out being reasonably specific.

From a labeling standard perspective, would it be better to perhaps maybe reduce the number and broaden them, including those particular areas, but I mean do we need to be or should we be this specific?

DR. RUNNER: This is Susan Runner.

I believe that the sponsor has developed the indications that it wishes to market the device as, and if you feel that there should be some

changes, you should recommend it. But these are the indications that they started the study with, and these are the indications that they've presented to us to evaluate.

CHAIRMAN HEFFEZ: Dr. Bertrand.

DR. BERTRAND: Peter Bertrand.

I thought earlier we addressed that. We had data for some of the indications, and we were going to make the recommendation that for labeling that we don't have enough data on some of these other indications as part of the labeling process.

Did I misunderstand that?

CHAIRMAN HEFFEZ: That is correct.

DR. BERTRAND: So I think that applies to what we're looking at in 6(a) as far as indications.

DR. BURTON: Richard Burton.

Would we then, Dr. Heffez, would we then take that existing list of 11 indications, look at the existing patients that meet those indications, and for those say that it is approved for those indications, and then for the ones for which there's

insufficient data to show correlation, then sort of make them a subset?

I'm not sure. How would that be worded?

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: I think at this point in time the panel could defer that to FDA for a more complete review after the panel meeting, if you so choose. I think it would be laborious to go over specific numbers at this point in time.

I do think that for this question though there was some discussion earlier about potential labeling for treating the patient for potential bruxes and more tooth contact, and that might be an addition that you might want to further discuss.

As I recall, Dr. Bertrand had mentioned that issue.

DR. BURTON: Dr. Burton.

I would agree with that, Dr. Bertrand, but in the contraindications, actually the last one, number nine, states that it is contraindicated in patients with severe hyperfunctional habits, e.g., clinching, grinding, et cetera.

So I'm not sure how we address it because they have sort of already said that you really -- you know, their contraindications say that you really shouldn't put them in those patients to begin with.

CHAIRMAN HEFFEZ: Dr. Runner.

DR. RUNNER: However, we've heard from Dr. Quinn that their patients had between 18 and 24 hours a day tooth contact. So that to me indicates some degree of bruxism.

DR. BURTON: Actually I think that regarding this item it should probably be moved up into the warnings as opposed to being in the paragraph. It should be listed numerically.

How do the panel members feel about that?

You have listed warnings, but I think one warning would be that emplacement of this device in patients with severe hyperfunctional habit, an undesirable outcome may occur, and I think that would be item number 617 in the one.

DR. RUNNER: I think there's some very

specific literature about what's a warning, what's a contraindication, and we can --

CHAIRMAN HEFFEZ: Look at that.

DR. RUNNER: -- work at that.

CHAIRMAN HEFFEZ: Okay, but at least leaving this, we can suggest that we should look at where it's localized in the document.

DR. RUNNER: Right.

CHAIRMAN HEFFEZ: The hyperfunctional habits.

DR. RUNNER: Right.

CHAIRMAN HEFFEZ: Yes?

DR. ANSETH: Kristi Anseth.

Also on the precautions, the number nine that talks about use of the system with filler material, and I thought that we had discussed this being a cementless system.

CHAIRMAN HEFFEZ: Correct. So that's something we should look at removing. Thank you.

I'd like to move to the second part of that, which would be the patient information, if we could look at that.

In the patient information, I notice the term glenoid fossa in one place and then fossa in another place. When it says what is a Walter Lorenz TMJ implant? It says, number two, fossa implant, and then when you go to what are the possible complications, it talks about glenoid fossa.

I think probably the patient might feel better with a diagram, for example, indicating what is the glenoid fossa and let them know it is a glenoid fossa. They may think it's two different terms.

Also, if you look at contraindications, you list active infection, but in the material for the physician, it says active or chronic infection, which is what are the contraindications for Walter Lorenz, patients with active infection, but contraindication for the physician is active or chronic infection. Just to be consistent.

1/11 ask the company to consider maybe active foreign body reaction. I don't see that really listed there, but it is a concern with people with current prostheses undergoing foreign body

reaction, that that should be treated before implanting a new device.

So I'm suggesting active infection, chronic infection, or foreign body, active foreign body reaction. I made those suggestions, but I'd like to hear from the panel how they feel.

Dr. Cochran.

DR. COCHRAN: It looks like the foreign body issue is addressed in number four and the possible complications under I believe that's the patient, under the patient information. It's not exactly what you said, but it at least addresses it.

CHAIRMAN HEFFEZ: That refers to the foreign body reaction to the material that they implanted.

DR. COCHRAN: Right.

CHAIRMAN HEFFEZ: But I'm referring to foreign body material on another implant that they're removing to put in.

Anybody else have any comments?

(No response.)

CHAIRMAN HEFFEZ: Okay. The foreign

body reaction I think should be placed also in the physician information.

All right. We'll move on then to 6(b). Please discuss the need for training and the type of training protocol that may be necessary for safe and effective use of this device.

If I could just summarize what's been said up to now, that the principles involved feel that training at one or two sites and expanding those sites as people are properly trained is necessary.

I think that they have an audiovisual tape that has not been furnished to the FDA, and that they will have a protocol through probably continuing education programs that they will offer.

I'd like to hear from the panel how they feel in general regarding this. Also, perhaps we should think about is it possible, that it is very easy to do this early on in the course of a product. Sometimes as the product gets distributed it becomes more and more difficult from the company's point of view, from a financial point of view from the